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L1: Entry 1 of 4

File: USPT

Oct 30, 2001

DOCUMENT-IDENTIFIER: US 6310076 B1

TITLE: Dihydropyridines and new uses thereof

## PCPR:

This application is a divisional of U.S. Ser. No. 09/098,699, filed Jun. 15, 1998 U.S. Pat. No. 6,211,198, which is divisional of U.S. Ser. No. 08/211,764 filed Feb. 23, 1996, now U.S. Pat. No. 5,767,131, issued Jun. 16, 1998, which is a 371 national stage filing of PCT/US94/03852, filed Apr. 5, 1994, which is a continuation-in-part of U.S. Ser. No. 08/166,367, filed Dec. 10, 1993, now abandoned, which is a continuation-in-part of U.S. Ser. No. 08/120,169, filed Sep. 10, 1993, now abandoned, which is a continuation-in-part of U.S. Ser. No. 08/043,212, filed Apr. 5, 1993, now abandoned, the contents of all of which are hereby incorporated by reference into this application.

## DEPR:

4,4-bis-(4-Methoxyphenyl)piperidine (9.01 g, 30.3 mmol, 1.00 equiv), 3-bromopropylamine hydrobromide (6.66 g, 30.3 mmol, 1.00 equiv) and potassium carbonate (5.02 g, 36.3 mmol, 1.20 equiv) were stirred in refluxing anhydrous 1,4-dioxane (200 mL) for 12 hours. After removal of dioxane, water (200 mL) was added and the pH was adjusted to 11-12 by addition of 1 N aqueous NaOH. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4.times.200 mL). The combined organic solutions were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by flash chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub> --MeOH--NH<sub>3</sub> (2 M in MeOH) 100:20:10) to give 6.50 g of 4,4-bis-(4-methoxyphenyl)piperidine and 2.70 g (25%, 90% after correction for recovered starting material) of 1-(3-aminopropyl)-4,4-bis-(4-methoxyphenyl)piperidine (colorless oil), which was characterized spectroscopically.

## DEPR:

A mixture of 5-carboxamido-2,6-diethyl-1,4-dihydro-4-(4-nitrophenyl)pyridine-3-carboxylic acid (300 mg, 0.869 mmol, 1.00 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (250.0 mg, 1.30 mmol, 1.50 equiv) and 4-dimethylaminopyridine (116.9 mg, 0.957 mmol, 1.10 equiv) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (18 mL) was stirred at room temperature under argon for 1 hour. A solution of 1-(3-aminopropyl)-4,4-bis-(4-methoxyphenyl)piperidine (369.6 mg, 1.04 mmol, 1.20 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) was injected, and the mixture was stirred at reflux for 6 hours. The mixture was cooled to room temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub> (180 mL), and washed with saturated aqueous NH<sub>4</sub>Cl (3.times.50 mL). The organic phase was dried over MgSO<sub>4</sub> and concentrated. The residue was purified by flash chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub> --MeOH-methanolic ammonia (2 M) 100:4:2 to 100:5:2.5) to afford 535 mg (90%) of 103 free base as a yellow solid, which was characterized spectroscopically. To a solution of this product (520 mg, 0.760 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added HCl in ether (1.0 M, 1.5 mL, 2.0 equiv). After removal of the solvents, the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) and added dropwise to ether (50 mL) with swirling to give, after filtration, 465 mg of yellow solid: m.p. 175.degree. C. (decomp.); Anal.

Calcd. for C.sub.39 H.sub.48 N.sub.5 O.sub.6.HCl.1.5 H.sub.2 O: C, 62.85; H, 6.90; N, 9.40. Found: C, 62.95; H, 6.80; N, 9.16.

DEPC:

4,4-bis- (4-Methoxyphenyl)piperidine

DEPC:

1-(3-Aminopropyl)-4,4-bis- (4-methoxyphenyl)piperidine

DEPC:

5-Carboxamido-2,6-diethyl-1,4-dihydro-3-{N-[3-(4,4-bis- (4-methoxyphenyl)piperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine hydrochloride (103)

DEPC:

2,6-Diethyl-1,4-dihydro-4-(3-methoxyphenyl)-3,5-bis(N-(3-(4,4-diphenylpiperidin-1-yl)propyl)carboxamido)-pyridine (112)

RLPN:

5767131

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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☐ 2. Document ID: US 6235759 B1

L1: Entry 2 of 4

File: USPT

May 22, 2001

DOCUMENT-IDENTIFIER: US 6235759 B1

TITLE: Dihydropyridinones and pyrrolinones useful as alpha 1A adrenoceptor antagonists

BSPR:

As shown in Scheme I, part c, aryl- and heteroaryl-acetonitriles can be treated with a base such as NaH or cesium carbonate and with bis-(2-chloroethyl)-tert-butoxycarbonylamine to afford the piperidine derivatives of type 7. Deprotection and alkylation as described before gives access to amines of type 8. Alkylation with other monoprotected amines of general formula Br(CR.sup.4 R.sup.5).sub.n NHBoc, followed by deprotection allows for the preparation of a diverse range of amines of type 8.

DEPR:

To a solution of bis-(2-chloroethyl)amine hydrochloride (10 g, 56.66 mmol) in 210 ml 2.5:1 dioxane:H.sub.2 O was added triethylamine (7.88 mL, 56.66 mmol). This solution was cooled to 0.degree. C. under argon, and Boc anhydride (14.96, 68.58 mmol) was added dropwise. This was stirred for 45 min, poured onto saturated sodium bicarbonate, and extracted with ethyl acetate. The combined organic layers were washed with saturated sodium chloride, dried with magnesium sulfate, and concentrated in vacuo to give the product.

DEPR:

To a solution of bis-(2-chloro-ethyl)-tert-butoxycarbonylamine (3.0 g, 12.39 mmol) in 75 mL of DMF was added 4-fluorobenzylacetonitrile (1.515 g, 11.27 mmol). This solution was cooled to 0.degree. C., and a 60% dispersion of sodium hydride was added portion wise (1.17 g, 29.25 mmol). The solution was stirred for 20 min, warmed to room temperature, then heated to 80.degree. C. for 24 h. It was poured onto water, and extracted with ethyl acetate. The combined organic layers were washed with saturated sodium chloride, dried with magnesium sulfate, and concentrated in vacuo. The crude material was passed through silica (25% ethyl acetate, hexane) to give the product.

DEPT:

Step A. Bis-(2-chloro-ethyl)-tert-butoxycarbonylamine

URPN:

5767131

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KMC	Draw Desc	Image
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☐ 3. Document ID: US 6211198 B1

L1: Entry 3 of 4

File: USPT

Apr 3, 2001

DOCUMENT-IDENTIFIER: US 6211198 B1

TITLE: Dihydropyridines and new uses thereof

PCPR:

This application is a divisional of U.S. Ser. No. 08/211,764, filed Feb. 23, 1996, now U.S. Pat. No. 5,767,131, issued Jun. 16, 1998, which is a 371 national stage filing of PCT/US94/03852, filed Apr. 5, 1994, which is a continuation-in-part of U.S. Ser. No. 08/166,367, filed Dec. 10, 1993, now abandoned, which is a continuation-in-part of U.S. Ser. No. 08/120,169, filed Sep. 10, 1993, now abandoned, which is a continuation-in-part of U.S. Ser. No. 08/043,212, filed Apr. 5, 1993, now abandoned, the contents of which are hereby incorporated by reference into this application.

DEPR:

4,4-bis-(4-Methoxyphenyl)piperidine. To a solution of AlCl<sub>3</sub> (26.0 g, 0.195 mmol, 6.00 equiv) in anhydrous anisole (100 mL) at 0.degree. C. under argon was added 4-piperidone hydrate hydrochloride (5.00 g, 32.5 mmol, 1.00 equiv). stirring was continued at 0.degree. C. for 3 hours and then at room temperature for 12 hours. The mixture was added cautiously to ice water (100 g of ice plus 50 mL of water). The aqueous phase was extracted with Et<sub>2</sub>O (3.times.50 mL) and the combined organic solutions were concentrated. The resulting white solid was dissolved in water (100 mL). This solution was basified to pH 11-12 by addition of 1N aqueous NaOH, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (250 mL+3.times.150 mL). The combined organic solutions were dried over MgSO<sub>4</sub> and concentrated to afford 9.38 g (97%) of colorless oil, which was characterized spectroscopically.

DEPR:

1-(3-Aminopropyl)-4,4-bis-(4-methoxyphenyl)piperidine. 4,4-bis-(4-Methoxyphenyl)piperidine (9.01 g, 30.3 mmol, 1.00 equiv), 3-bromopropylamine hydrobromide (6.66 g, 30.3 mmol, 1.00 equiv) and potassium carbonate (5.02 g, 36.3 mmol, 1.20 equiv) were stirred in refluxing anhydrous 1,4-dioxane (200 mL) for 12 hours. After removal of dioxane, water (200 mL) was added and the pH was adjusted to 11-12 by addition of 1N aqueous NaOH. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4.times.200 mL). The combined organic solutions were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by flash chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>--MeOH--NH<sub>3</sub> (2M in MeOH) 100:20:10) to give 6.50 g of 4,4-bis-(4-methoxyphenyl)piperidine and 2.70 g (25%, 90% after correction for recovered starting material) of 1-(3-aminopropyl)-4,4-bis-(4-methoxyphenyl)piperidine (colorless oil), which was characterized spectroscopically.

DEPR:

5-Carboxamido-2,6-diethyl-1,4-dihydro-3-{N-[3-(4,4-bis-(4-methoxyphenyl)piperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine hydrochloride (103). A mixture of 5-carboxamido-2,6-diethyl-1,4-dihydro-4-(4-nitrophenyl)pyridine-3-carboxylic acid (300 mg, 0.869 mmol, 1.00 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (250.0 mg, 1.30

mmol, 1.50 equiv) and 4-dimethylaminopyridine (116.9 mg, 0.957 mmol, 1.10 equiv) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (18 mL) was stirred at room temperature under argon for 1 hour. A solution of 1-(3-aminopropyl)-4,4-bis-(4-methoxyphenyl)piperidine (369.6 mg, 1.04 mmol, 1.20 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) was injected, and the mixture was stirred at reflux for 6 hours. The mixture was cooled to room temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub> (180 mL), and washed with saturated aqueous NH<sub>4</sub>Cl (3 times, 50 mL). The organic phase was dried over MgSO<sub>4</sub> and concentrated. The residue was purified by flash chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub> -- MeOH-methanolic ammonia (2M) 100:4:2 to 100:5:2.5) to afford 535 mg (90%) of 103 free base as a yellow solid, which was characterized spectroscopically. To a solution of this product (520 mg, 0.760 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added HCl in ether (1.0M, 1.5 mL, 2.0 equiv). After removal of the solvents, the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) and added dropwise to ether (50 mL) with swirling to give, after filtration, 465 mg of yellow solid: m.p. 175.degree. C. (decomp.); Anal. Calcd. for C<sub>39</sub>H<sub>48</sub>N<sub>5</sub>O<sub>6</sub>.HCl.1.5 H<sub>2</sub>O: C, 62.85; H, 6.90; N, 9.40. Found: C, 62.95; H, 6.80; N, 9.16.

## DEPR:

2,6-Diethyl-1,4-dihydro-4-(3-methoxyphenyl)-3,5-bis(N-(3-(4,4-diphenylpiperidin-1-yl)propyl)carboxamido)-pyridine (112). A mixture of 2-cyanoethyl propionylacetate (1.00 g, 5.91 mmol), m-anisaldehyde (1.0 mL, d 1.119, 8.22 mmol) and 3-aminocrotonamide (0.89 g, 8.89 mmol) in EtOH (9 mL) was heated at reflux overnight. Then the solvent was evaporated to give an oily residue which was suspended in chloroform and flash chromatographed over silica gel (100 g). Elution with EtOAc/Hexane (1:2, 1:1 and 3:1) gave a yellow oil (336 mg). It was dissolved in EtOH (1.5 mL) and treated with NaOH (74 mg, 1.85 mmol) in water (1 mL). The solution was stirred at room temperature overnight and then washed twice with CH<sub>2</sub>Cl<sub>2</sub>. Acidification of the basic layer with 5% HCl gave a precipitate which was filtered off and washed with water and EtOAc to afford an off-white solid (118 mg, 6% yield).

## RLPN:

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☐ 4. Document ID: US 5767131 A

DOCUMENT-IDENTIFIER: US 5767131 A  
TITLE: Dihydropyridines and new uses thereof

## DEPR:

4,4-bis-(4-Methoxyphenyl)piperidine (9.01 g, 30.3 mmol, 1.00 equiv), 3-bromopropylamine hydrobromide (6.66 g, 30.3 mmol, 1.00 equiv) and potassium carbonate (5.02 g, 36.3 mmol, 1.20 equiv) were stirred in refluxing anhydrous 1,4-dioxane (200 mL) for 12 hours. After removal of dioxane, water (200 mL) was added and the pH was adjusted to 11-12 by addition of 1 N aqueous NaOH. The mixture was extracted with CH.sub.2 Cl.sub.2 (4.times.200 mL). The combined organic solutions were dried over MgSO.sub.4 and concentrated. The residue was purified by flash chromatography (SiO.sub.2, CHCl.sub.3 -MeOH-NH.sub.3 (2M in MeOH) 100:20:10) to give 6.50 g of 4,4-bis-(4-methoxyphenyl)piperidine and 2.70 g (25%, 90% after correction for recovered starting material) of 1-(3-aminopropyl)-4,4-bis-(4-methoxyphenyl)piperidine (colorless oil), which was characterized spectroscopically.

## DEPR:

A mixture of 5-carboxamido-2,6-diethyl-1,4-dihydro-4-(4-nitrophenyl)pyridine-3-carboxylic acid (300 mg, 0.869 mmol, 1.00 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (250.0 mg, 1.30 mmol, 1.50 equiv) and 4-dimethylaminopyridine (116.9 mg, 0.957 mmol, 1.10 equiv) in anhydrous CH.sub.2 Cl.sub.2 (18 mL) was stirred at room temperature under argon for 1 hour. A solution of 1-(3-aminopropyl)-4,4-bis-(4-methoxyphenyl)piperidine (369.6 mg, 1.04 mmol, 1.20 equiv) in CH.sub.2 Cl.sub.2 (12 mL) was injected, and the mixture was stirred at reflux for 6 hours. The mixture was cooled to room temperature, diluted with CH.sub.2 Cl.sub.2 (180 mL), and washed with saturated aqueous NH.sub.4 Cl (3.times.50 mL). The organic phase was dried over MgSO.sub.4 and concentrated. The residue was purified by flash chromatography (SiO.sub.2, CHCl.sub.3 -MeOH-methanolic ammonia (2M) 100:4:2 to 100:5:2.5) to afford 535 mg (90%) of 103 free base as a yellow solid, which was characterized spectroscopically. To a solution of this product (520 mg, 0.760 mmol, 1.0 equiv) in CH.sub.2 Cl.sub.2 (5 mL) was added HCl in ether (1.0M, 1.5 mL, 2.0 equiv). After removal of the solvents, the residue was dissolved in CH.sub.2 Cl.sub.2 (8 mL) and added dropwise to ether (50 mL) with swirling to give, after filtration, 465 mg of yellow solid: m.p. 175.degree. C. (decomp.); Anal. Calcd. for C.sub.39 H.sub.48 N.sub.5 O.sub.6.HCl.1.5 H.sub.2 O: C, 62.85; H, 6.90; N, 9.40. Found: C, 62.95; H, 6.80; N, 9.16.

## DEPC:

4,4-bis-(4-Methoxyphenyl)piperidine

## DEPC:

1-(3-Aminopropyl)-4,4-bis-(4-Methoxyphenyl)piperidine

## DEPC:

5-Carboxamido-2,6-diethyl-1,4-dihydro-3-{N-[3-(4,4-bis-(4-methoxyphenyl)piperidin-1-yl)propyl]}carboxamido}-4-(4-nitrophenyl)pyridine hydrochloride (103)

## DEPC:

2,6-Diethyl-1,4-dihydro-4-(3-methoxyphenyl)-3,5-bis(N-(3-(4,4-diphenylpiperidin-1-yl)propyl)carboxamido)-pyridine (112)

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